

THE EFFECT OF PROTEOLYTIC ENZYMES ON THE DISPOSITION OF CYCLOPHOSPHAMIDE

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Oral administration of proteolytic enzymes has been reported to enhance the absorption and tissue penetration of several drugs including penicillin (Wohlmann & others, 1969) and isoniazid (Wisniewski, 1972). A combination of proteolytic enzymes with cyclophosphamide (CP) is claimed to improve therapy (Silva, personal communication) compared with CP alone when used for the treatment of solid tumours. Therefore the effect of a combination of trypsin and chymotrypsin in a ratio of 6:1 respectively (Chymoral) on the disposition of CP in patients was investigated.

Four patients, Group A, received 50 mg of CP three times a day for 14 days. On day 15 plasma samples were collected just before the morning dose and at 1, 2, 3, 6, 9 and 12 h after the dose. No more CP was taken that day. On day 16 treatment was continued, the patients now taking Chymoral tablets concomitantly with the CP. The sampling procedure was repeated on day 31 of the study.

Three control patients (Group D) received no Chymoral during the second period of treatment. Plasma samples were assayed for CP by the GLC method of Pantarotto & others (1974) which was modified to increase selectivity and sensitivity and for alkylating metabolites by the method of Friedman & Boger (1961). The results are summarized in Table 1.

Table 1. Mean disposition parameters for cyclophosphamide and alkylating metabolites.

Group	Cyclophosphamide				Alkylating Metabolites	
	Treatment AUC ¹	CP t _{1/2} (h)	CP + Chymoral AUC	CP + Chymoral t _{1/2} (h)	CP AUC	CP + Chymoral AUC
A	30.7 ± 16	6.5 ± 2.5	32.6 ± 18	5.6 ± 1	17.9 ± 4	17.5 ± 3
D	15.5 ± 5	6.7 ± 2	19 ± 3	5.8 ± 3.1	24.2 ± 3.6	29.5 ± 8.2

¹AUC = Area under plasma level/time curve 0-8 h µg/ml h.

The half life of CP was shorter after Chymoral in three patients, but it was also reduced in two control patients. The clearance of CP is related to the AUC value by $Cl = F \cdot \text{Dose}/\text{AUC}$ (0-8 h). Each patient acted as his/her own control, so, if it is assumed that the absorption characteristics of the individual do not change between treatments, errors in assuming $F = 1$ affect both values for clearance equally. Therefore AUC is proportional to clearance. No significant difference in AUC was found after Chymoral treatment as judged by a paired t test ($P = 0.05$). Similarly, no significant difference was found in the AUC of metabolites after Chymoral treatment. Since no major change in half life of CP was found it may be concluded that distribution volume is unaffected. Therefore it can be seen that proteolytic enzymes have little effect on the disposition of CP. The reported improvement in therapy must be due to some other effect.

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